The Electrophysiologic Effects of Propafenone Hydrochloride in the Neonatal Canine

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ABSTRACT. The electrophysiologic effects of the new antiarrhythmic agent, propafenone, were investigated in 10 mongrel canine neonates, ages 5 to 11 days. Utilizing standard His bundle recording and stimulation techniques, assessments of sinus and atrioventricular (AV) node function and atrial, AV nodal, and ventricular refractory periods were performed prior to (control) and after cumulative intravenous doses of 1, 2, and 4 mg/kg of propafenone. Propafenone depressed the spontaneous heart rate and prolonged the postatrial pacing recovery times. AV nodal function was depressed as manifested by Wenckebach periodicity occurring at slower pacing rates, increases in AV nodal conduction time, and increases in AV nodal refractoriness. Atrial and ventricular refractory periods were prolonged significantly in a dose-dependent fashion. Prolongation of the His-Purkinje conduction time occurred at the highest dose. Thus, propafenone exerts a generalized depressant effect on neonatal myocardial conduction and refractoriness which suggests that this agent may be useful in the therapy of atrial and ventricular dysrhythmias in the immature heart. (*Pediatr Res* 22: 50-54, 1987)

Abbreviations

SNRT, sinus node recovery time
ERP, effective refractory period
CSNRT, corrected sinus node recovery time
% SNRT; percent sinus node recovery time
ANOVA, analysis of variance
AVNERP, AV node effective refractory period
AVNFRP, AV node functional refractory period

Propafenone is a new antiarrhythmic agent (type IC) which has proven to be clinically effective in suppressing a wide variety of arrhythmias including ventricular and supraventricular arrhythmias as well as arrhythmias associated with the Wolff-Parkinson-White syndrome (1-7). In children, propafenone has been reported to be effective in treating a variety of arrhythmias including postoperative junctional ectopic tachycardia (7, 8). Nevertheless, to date there is very limited information concerning the use of propafenone in treating young infants with cardiac

arrhythmias. Furthermore, the electrophysiologic effects of type IC agents in general have not been defined in the immature heart. Current information available concerning the effects of propafenone have been derived from studies of isolated cardiac tissues (9, 10) and studies in adult humans (2, 6, 11) and adult dogs (12). We undertook this study to assess the electrophysiologic responses of the immature mammalian heart to incremental doses of this new antiarrhythmic agent.

METHODS

Ten mongrel canine neonates, ages 5 to 11 days, were studied. All animals were anesthetized with sodium pentobarbital, 30 mg/kg intraperitoneally, and supplemented intravenously as needed to maintain anesthesia. The dogs were mechanically ventilated with a Harvard respirator.

Surface electrocardiographic lead II and femoral artery blood pressure were constantly monitored. Three electrode catheters were used for intracardiac electrogram recordings and stimulation and were positioned utilizing fluoroscopic visual guidance. A no. 5 French quadripolar catheter was positioned in the high right atrium using a right femoral vein approach; a no. 5 French quadripolar catheter was positioned in the right ventricular apex using a right jugular vein approach and, in order to record the His bundle electrogram, a no. 4 French tripolar catheter was positioned in the noncoronary aortic cusp via the left carotid artery. Intracardiac electrograms were amplified at a filter setting of 40-500 Hz and displayed with the surface ECG on a multi-channel oscilloscope (Electronics for Medicine, DR-6). Recordings were made on direct writing paper (Kodak Linagraph Paper 2201) at a paper speed of 100 mm/s.

Artificial stimulation was performed utilizing a programmable digital stimulator (Medtronic, model 5325). Electrical impulses of 2 ms duration were delivered at twice diastolic threshold. Atrial and ventricular single extrastimulation was performed by introducing a premature beat (S_2) after every eighth paced beat of a paced cycle length (S_1S_1) at 10 ms decrements until atrial or ventricular refractoriness was reached. Rapid atrial and ventricular pacing for 30 and 15 s, respectively, was performed starting at a rate slightly above the resting heart rate and repeated using 25 bpm increments until Wenckebach periodicity (antegrade during atrial pacing, retrograde during ventricular pacing) was observed.

The entire electrophysiologic protocol was performed prior to the administration of propafenone. This study served as the control state. The protocol could be completed in less than 8 min. Propafenone was then administered intravenously at a dose of 1 mg/kg and, 15 min later, the entire electrophysiologic protocol was repeated. At similar time intervals, two additional doses of propafenone (1 and 2 mg/kg) were administered. After

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Table 3. Effects of propafenone*

		Propafenone dose (mg/kg)			
		C	1.0	2.0	4.0
PA	Mean	5	6	6	6
	SD	6	6	6	6
AH	Mean	54	57	61†	63‡
	SD	7	8	8	7
HV	Mean	18	19	19	25‡
	SD	3	2	2	3
AERP	Mean	63	76	88†	117‡
	SD	12	12	18	27
AFRP	Mean	101	114	126†	154‡
	SD	17	16	16	33
AVNERP	Mean	144	164	185†	203‡
	SD	36	37	36	27
AVNFRP	Mean	186	202	225†	241‡
	SD	26	23	28	23
VERP	Mean	150	164†	175	194‡
	SD	12	11	13	13
VFRP	Mean	172	188†	198	213‡
	SD	14	13	13	9

*C, control; PA, intraatrial conduction time; AH, AV nodal conduction time; HV, His-Purkinje conduction time; AERP, atrial effective refractory period; AFRP, atrial functional refractory period; VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period.

† $p < 0.01$ Scheffé analysis.

‡ $p < 0.001$ ANOVA for repeated measurements.

Fig. 2. Atrial effective (AERP) and functional (AFRP) refractory periods (ms) during the control state (C) and after each cumulative dose of propafenone. A significant dose-dependent increase in both atrial effective and functional refractory periods is observed.

144 $\pm$ 36 to 203 $\pm$ 27 ms while the AVNFRP increased from 186 $\pm$ 26 to 241 $\pm$ 23 ms after the last dose of propafenone, ANOVA $p < 0.001$, Scheffé $p < 0.01$ at 2 mg/kg dose (Fig. 3). In addition to altering AV nodal refractoriness, propafenone depressed AV nodal conduction. This was manifested not only by the dose-dependent prolongation in the AH interval described above but also by changes in the paced heart rate at which Wenckebach periodicity was observed. Prior to the administration of propafenone Wenckebach periodicity was observed at atrial pacing rates of 327 $\pm$ 53 bpm while following propafenone Wenckebach occurred at an average heart rate of 255 $\pm$ 28 bpm, ANOVA $p < 0.001$, Scheffé $p < 0.05$ at 1 mg/kg (Fig. 4).

Retrograde conduction (ventriculoatrial conduction in re-

Fig. 3. Effect of propafenone on AVNERP and AVNFRP. A dose-dependent increase in AV nodal refractory periods occurs following propafenone.

Fig. 4. Effect of propafenone on the paced heart rate resulting in AV dose-dependent decrease in resting heart rate is observed. nodal Wenckebach.

sponse to ventricular pacing) was documented in eight of the 10 puppies. Retrograde Wenckebach periodicity also occurred at slower heart rates following the administration of propafenone (control 300 $\pm$ 61 bpm, postpropafenone 225 $\pm$ 33 bpm, ANOVA $p < 0.001$).

Ventricular refractory periods (Table 3). Propafenone resulted in significant changes in ventricular refractoriness. Ventricular effective and functional refractory periods both increased in a dose-dependent fashion. The ventricular effective refractory periods increased from 150 $\pm$ 12 to 194 $\pm$ 13 ms following propafenone while the functional refractory period increased from 172 $\pm$ 14 to 213 $\pm$ 9 ms, ANOVA $p < 0.001$ Scheffé $p < 0.01$ at 1 mg/kg dose (Fig. 5). While propafenone significantly increased ventricular muscle refractoriness, AV nodal refractoriness, and atrial muscle refractoriness, the magnitude of the changes, expressed as a percent increase over the control, were greater in the immature atrium (AERP 85% increase, AFRP 52% increase) than either the ventricle (VERP 29% increase, VFRP 24% increase) or AV node (AVNERP 40% increase, AVNFRP 30% increase).

each dose, a complete electrophysiologic study was performed. Thus, the total cumulative dose of intravenous propafenone evaluated was 4 mg/kg.

Definition of terms. Electrophysiologic measurements were performed according to standard definitions (13) and are summarized below. SNRT—the interval from the last paced atrial depolarization to the first sinus return cycle length. ERP of the atrium—the longest S_1S_2 that failed to result in an atrial depolarization. ERP of the AV node—the longest A_1A_2 that failed to result in a His deflection. ERP of the ventricle—the longest S_1S_2 that failed to result in a ventricular depolarization. FRP of the atrium—the shortest A_1A_2 in response to any S_1S_2 . FRP of the AV node—the shortest H_1H_2 in response to any A_1A_2 . FRP of the ventricle—the shortest V_1V_2 in response to any S_1S_2 . Intraatrial conduction (PA), AV nodal conduction (AH), His-Purkinje system conduction (HV) times and measurements of %SNRT, and CSNRT were measured according to standard methods. All electrophysiologic values (except %SNRT) were expressed in ms.

Statistical analysis. Electrophysiologic and hemodynamic parameters were expressed as a mean value (m) $\pm$ 1 SD. Statistical evaluation of the effects of drug administration was assessed by applying an ANOVA for repeated measurements. For all parameters, a p value of equal to or less than 0.05 was required to indicate statistical significance. Whenever ANOVA proved significant, a Scheffé analysis was performed to determine the lowest propafenone dose at which a significant ($p < 0.05$) change from control occurred.

RESULTS

Heart rate and blood pressure (Table 1). Over the entire dosing protocol propafenone resulted in a 20% decrease in the resting heart rate. The control heart rate was 175 ± 18 bpm which decreased to 163 ± 20 bpm following the first dose, 154 ± 21 bpm following the second dose, and 142 ± 16 bpm following the last propafenone dose (ANOVA $p < 0.001$, Scheffé $p < 0.05$ at 1 mg/kg dose) (Fig. 1). The systolic and diastolic blood pressures remained unchanged throughout the study.

Sinus node automaticity (Table 2). As mentioned above, there was a dose-dependent decrease in the spontaneous heart rate. In addition, propafenone resulted in a proportional prolongation of the SNRT from a control value of 418 ± 45 to 460 ± 46 ms after the first dose, 510 ± 53 ms following a second dose and 555 ± 58 ms following the third dose (ANOVA $p < 0.001$, Scheffé $p < 0.05$ at 1 mg/kg dose). Changes in %SNRT were negligible due to the proportional prolongation of SNRT and the sinus cycle length. The CSNRT, however, increased 65% over the control value following the last propafenone dose.

Basic conduction intervals (Table 3). Propafenone caused no significant change in the PA interval. Propafenone resulted in a modest but significant prolongation of the AV nodal conduction time (AH interval control 54 ± 7 ms; 63 ± 7 ms post last dose).

Table 1. Effects of propafenone*

		Propafenone dose (mg/kg)			
		C	1.0	2.0	4.0
BCL (ms)	Mean	346	372	396†	428‡
	SD	35	43	53	49
HR (bpm)	Mean	175	163§	154	142‡
	SD	18	20	21	16
BPS (mm Hg)	Mean	63	70	68	63
	SD	10	15	13	11
BPD (mm Hg)	Mean	29	32	31	29
	SD	8	12	11	10

* C, control; BCL, basic cycle length; HR, resting heart rate; BPS, systolic blood pressure; BPD, diastolic blood pressure.

† $p < 0.01$ Scheffé analysis.

‡ $p < 0.001$ ANOVA for repeated measurements.

§ $p < 0.05$.

Fig. 1. Resting heart rate (bpm) is plotted as a function of cumulative propafenone dose (C, control, 1.0, 2.0, and 4.0 mg/kg). A significant dose-dependent decrease in resting heart rate is observed.

Table 2. Effects of propafenone*

		Propafenone dose (mg/kg)			
		C	1.0	2.0	4.0
SNRT (ms)	Mean	418	460†	510	555‡
	SD	45	46	53	58
% SNRT	Mean	123	126	131	129
	SD	8	13	14	14
CSNRT (ms)	Mean	76	92	116†	126‡
	SD	25	39	43	48
WENCK (bpm)	Mean	327	297†	280	255‡
	SD	53	36	39	28
RETRO-WENCK (bpm)	Mean	300	266†	247	225‡
	SD	61	44	41	33

* C, control value; SNRT, sinus node recovery time; WENCK, paced heart rate at which antegrade AV nodal Wenckebach occurred; RETRO-WENCK, paced ventricular heart rate at which ventriculoatrial Wenckebach periodicity occurred.

† $p < 0.05$ Scheffé analysis.

‡ $p < 0.001$ ANOVA for repeated measurements.

The HV interval remained the same after the first and second doses of propafenone (control 18 ± 3 ms; 19 ± 2 ms post second dose). However, following the highest propafenone dose the HV interval increased from 19 ± 2 to 25 ± 3 ms. This increase was significant by the Scheffé ($p < 0.01$) analysis.

Atrial refractory periods (Table 3). Atrial refractoriness was significantly altered by propafenone in a dose-dependent fashion. There were significant increases in both the atrial effective and atrial functional refractory periods. The atrial effective refractory period increased from a control of 63 ± 12 to 117 ± 27 ms after the last dose of propafenone (ANOVA $p < 0.001$). Similarly, the atrial functional refractory period increased from a control value of 101 ± 17 to 154 ± 33 ms at the end of the dosing protocol (ANOVA $p < 0.001$) (Fig. 2). In both instances the Scheffé analysis revealed a significant change occurring at the 2 mg/kg propafenone dose.

AV nodal refractory periods and Wenckebach periodicity (Tables 2 and 3). AV nodal effective and functional refractory periods could be measured in seven of the puppies. In the remaining three puppies, the atrial refractory period was reached before the AV nodal refractory period could be determined. In the seven puppies in whom AV nodal refractoriness could be assessed, propafenone produced dose-dependent increases in both the AVNERP and AVNFRP. The AVNERP increased from

Fig. 5. Ventricular effective (VERP) and functional (VFRP) refractory periods plotted as a function of cumulative propafenone dose. There is a dose-dependent increase of both effective and functional refractory periods.

DISCUSSION

Propafenone is an antiarrhythmic agent with predominantly membrane stabilizing properties. While there is evidence to suggest that propafenone acts to some extent as a β -2 and calcium channel blocker (9–11), it is generally thought that it is the ability of propafenone to block the fast sodium current that is responsible for much of its antiarrhythmic efficacy. As an inhibitor of the fast sodium channel, propafenone is broadly considered to be similar to other class I antiarrhythmic agents. In recent years, however, it has been recognized that within the group of class I antiarrhythmic drugs, significant differences exist in the relative abilities of the various agents to lengthen tissue refractoriness, depress conduction, and prolong action potential repolarization (14). Therefore, a new classification of class I agents has emerged in which three subgroups are recognized: the first group (type IA) includes such agents as quinidine and procainamide. These drugs lengthen tissue refractoriness and prolong action potential duration. The second group (type IB), of which lidocaine is an example, has limited effects on conduction and shortens action potential duration. The third group (type IC) is composed largely of newer antiarrhythmic agents such as encainide, flecainide, and propafenone. These agents are characterized by a propensity to slow conduction at low concentrations and produce changes in tissue refractoriness but not to significantly alter action potential duration.

Several clinical studies have confirmed the efficacy of propafenone against a variety of both ventricular and supraventricular arrhythmias in the adult population (1–6). While experience with propafenone in the pediatric age group is very limited the few available reports do suggest that propafenone may be a potentially important agent in the therapy of cardiac arrhythmias in the infant and child. Weber *et al.* (7) reported their experience with propafenone in 28 infants and children (including four children less than 15 kg). In their study, the efficacy of intravenous and oral propafenone was evaluated in 20 children with supraventricular tachycardia, five with atrial flutter, two with premature ventricular contractions, and one with junctional tachycardia. After a mean follow-up of 1.6 yr, 27 of 28 children were either free of arrhythmias (20 patients) or improved (seven patients). More recently, Garson *et al.* (8) reported that propafenone successfully controlled the ventricular rate in four pediatric patients, ages 11 days to 9 months, with postoperative junctional ectopic tachycardia, an arrhythmia usually refractory

to medical management. These reports suggest that propafenone may be useful in the therapy of refractory cardiac arrhythmias in the pediatric population and mandate that studies defining the pharmacodynamics of propafenone in the immature heart be performed.

In the present study, we have determined the electrophysiologic and hemodynamic responses of the immature mammalian heart to incremental intravenous doses of propafenone. In the neonatal canine, propafenone resulted in a significant dose-dependent increase in the sinus cycle length and prolonged the SNRT and CSNRT. While some investigators have ascribed a slowing of the sinus cycle length to propafenone's purported β inhibitory effects (4), others have suggested that the β sympatholytic actions of propafenone are only mild (11, 15). That the effects of propafenone on the neonatal canine sinus node are, to a large extent, a direct effect rather than due to β blockade is suggested by the observation that propafenone produced a greater slowing of the sinus cycle length (23% increase) and a greater prolongation of the CSNRT (65% increase) than that observed following the administration of intravenous propranolol in the same neonatal model (sinus cycle length increase 14%; CSNRT, no significant change) (16). The relative sinus tachycardia described in the adult dog following the administration of intravenous propafenone has been thought to be the result of a reflex tachycardia occurring in response to a modest fall in the blood pressure (12). In our neonatal puppies, propafenone was well tolerated and no significant changes in either systolic or diastolic blood pressure were observed.

The effects of propafenone on the neonatal AV node consisted of a decrease in the paced heart rate resulting in AV nodal Wenckebach, an increase in the AH interval, and a prolongation of the AV nodal refractory periods. An increase in AV nodal refractoriness similar in magnitude to the increases observed in our study (AVNFRP increase 29%) have been previously reported in the adult dog (AVNFRP increase 24%) (12). The marked effects of propafenone on AV nodal function is in contrast to the reported effects of both type IB agents in the adult canine (12) and type IA agents (procainamide) in the (older) puppy (17). In the latter study, no significant changes in the refractory periods of the specialized conduction system were observed following intravenous procainamide. In the present study, not only were AV nodal conduction times increased by propafenone but also His Purkinje conduction times, although at higher doses.

Our data also demonstrate that in the neonatal canine heart, propafenone results in dose-dependent increases in both atrial and ventricular myocardial refractoriness. In this study, the greatest changes in refractoriness were observed in atrial muscle refractoriness (ERP 85% increase; FRP 52% increase). The increases in both atrial and ventricular muscle refractoriness in the present study were quite similar in direction and magnitude to the changes reported in the neonatal canine in response to the potent class III antiarrhythmic agent amiodarone (18) and far greater than that observed in response to propranolol (16). Thus, in the neonatal heart, propafenone has significant effects on both atrial and ventricular refractoriness.

In comparing our findings with the effects of propafenone reported previously in adult canines (12), it is clear that while certain similarities are observed (*e.g.* the effect on AV nodal function) there do appear to be certain differences. Specifically, both the prolongation of the HV interval and ventricular muscle refractoriness observed in the neonate were not observed in adult dogs given a similar propafenone dose (4 mg/kg). On the other hand, we did not observe the significant changes in intraatrial conduction described in the adult dog. While it is not possible to fully explain these apparent differences it is important to describe them and to consider the possibility that the neonate may respond somewhat differently to this new antiarrhythmic agent. It is likely that developmental differences in action potential characteristics and possibly differences in cardiac autonomic

function may be important factors in determining the differences in responsiveness of the neonatal heart to propafenone.

In conclusion, our data demonstrate that propafenone is well tolerated in the neonatal canine and exerts a generalized depressant effect on the myocardium and conduction system. These changes include alterations of sinus node automaticity, AV nodal conduction and, at higher doses, His Purkinje conduction. Significant increases are observed in tissue refractoriness including AV node, ventricle, and atrium. This suggests that propafenone may have a role in the management of a variety of cardiac arrhythmias in the young pediatric population.

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